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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,308	01/29/2004	Rosana Kapeller-Libermann	MPI99-193CN2M	5472

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MILLENNIUM PHARMACEUTICALS, INC.
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CAMBRIDGE, MA 02139

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 04/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,308	KAPELLER-LIBERMANN ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12,14-20 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *12,14 and 19* is/are rejected.

7)☐ Claim(s) *15-18 and 20* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 1/12/06.

Claims 13, 21, and 23 were canceled.

Claims 12, 14-20, and 22 remain pending and under consideration in this Office Action.

Information Disclosure Statement

An information disclosure statement was received and entered on 1/12/06. the references were considered.

Drawings

The drawings filed 1/24/02 are acceptable for the purpose of examination.

Compliance with Sequence Rules

Applicant's amendment filed 1/12/06 placed the application in compliance with the requirements of 37 CFR 1.821 through 1.825.

Claim Objections

Applicant's amendment filed 1/12/06 overcame the objections of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description

Claims 12, 14, and 19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 12, 14, and 19 are directed to polypeptides with any aminopeptidase activity, wherein the polypeptide comprises an amino acid sequence at least 95% identical to SEQ ID NO:1, or wherein the polypeptide comprises an amino acid sequence encoded by a nucleic acid at least 90% identical to SEQ ID NO:2.

SEQ ID NO:1 is an aminopeptidase B (ApB). The prior art teaches that these enzymes catalyze the removal of N-terminal arginine and lysine residues. See Fukasawa et al (J. Biol. Chem. 271(48): (1996), page 30731, column 1, lines 5-10).

A wide variety of aminopeptidases is known in the art, and these enzymes catalyze different reactions. For example, the specification exemplifies amino peptidases that remove N-terminal methionines as well as aminopeptidases that are specific for arginine, leucine, and D-amino acids (see page 2, lines 9-14). It is clear to those of ordinary skill in the art that the specificity of a given aminopeptidase is dependent on its structure. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific

reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As such one of skill in the art could not conclude that Applicant was in possession of the genus of polypeptides comprising 95% sequence identity to SEQ ID NO:1, ***and*** the ability to cleave any N-terminal amino acid from any polypeptide.

Response to Arguments

Applicant's arguments filed 1/12/06 have been fully considered but they are not persuasive.

Applicant addresses the written description rejection at pages 7-9 of the response, arguing essentially that the rejection is overcome by limitation of the claims to polypeptides either at least 95% identical to SEQ ID NO:1 or encoded by nucleic acids at least 95% identical to SEQ ID NO:2. Applicant expresses the opinion at page 8, first full paragraph, that the knowledge and level of skill in the art would allow one of ordinary skill to envision the claimed invention. Applicant also expresses the opinion in the sentence bridging pages 8 and 9 that the "recitation of a predictable structure of at least 95% sequence identity to SEQ ID NO: 1 is sufficient to satisfy the written description requirement." No evidence is provided in support of these opinions. Instead, Applicant relies for support on Example 14 of the Written Description Guidelines. However, Example 14 is not analogous to the instant situation. Example 14 relates to a protein having at least 95% sequence identity to SEQ ID NO:3, wherein the protein catalyzes the interconversion of A and B. The instant claims differ in at least two ways. First, the subgenus drawn to proteins encoded by nucleic acids that are 95% identical to SEQ ID

NO:2 allows for proteins far less than 95% identical to SEQ ID NO:1. SEQ ID NO:2 is 2459 bases in length. Five percent of 2459 is about 123, so one could alter 123 of the 650 codons encoding SEQ ID NO:1 to obtain a protein that is only about 81% identical to SEQ ID NO:1. This is substantially broader than the genus depicted in Example 14. Second, Example 14 requires that the protein must have a specific chemical activity, i.e. interconversion of A and B. In contrast the instant claims require only "aminopeptidase activity" broadly, even though the specification identifies the claimed protein as an aminopeptidase B. As discussed above, aminopeptidases B catalyze the removal of N-terminal arginine and lysine residues. See Fukasawa et al (J. Biol. Chem. 271(48): (1996), page 30731, column 1, lines 5-10). Note that the instant specification exemplifies amino peptidases that remove N-terminal methionines as well as aminopeptidases that are specific for arginine, leucine, and D-amino acids (see page 2, lines 9-14). As a result the claims embrace proteins with any aminopeptidase activity, not just removal of N-terminal arginine and lysine residues. Therefore the instant situation is nonanalogous to Example 14 which recites a specific chemical reaction. Furthermore, the specification discloses no example of any aminopeptidase that is greater than 81% identical to SEQ ID NO:1, or greater than 95% identical to SEQ ID NO:1, that has any activity other than removal of N-terminal arginine and lysine residues. Accordingly one of skill in the art could not conclude that Applicant was in possession of such aminopeptidases. For these reasons the rejection is maintained.

Enablement

Claims 12, 14, and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polypeptides comprising SEQ ID NO:1 or fragments of SEQ ID NO:1, wherein the fragments have the amino peptidase activity of SEQ ID NO:1, does not reasonably provide enablement for sequence variants of SEQ ID NO:1, or sequence variants of fragments of SEQ ID NO:1, wherein the variants have any aminopeptidase activity broadly. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Claims 12 and 19 are drawn in part to polypeptides with aminopeptidase activity that are encoded by nucleic acid sequences that are at least 95% identical to the nucleic acid sequence of SEQ ID NO:2. SEQ ID NO:2 is a 2459 nucleotides in length, so the claims allow 123 nucleotide alterations in SEQ ID NO:2. SEQ ID NO:2 encodes a polypeptide of 650 amino acids. If each nucleotide alteration occurred in the second base of a codon in the open reading frame of SEQ ID NO:2, then the resulting polypeptides would be only 81% identical to SEQ ID NO:1.

Claim 14 is drawn to polypeptides that are 95% identical to SEQ ID NO:1.

The prior art teaches a polypeptide, rat aminopeptidase B, that is 88.6% identical to SEQ ID NO:1. See Fukasawa et al (J. Biol. Chem. 271(48): (1996). Fukasawa et al (Biochem. J. 339: 497-502, 1999) taught that aminopeptidase B is a zinc metalloprotease comprising a characteristic $HEXXHX_{18}E$ zinc binding motif. Fukasawa (1999) showed that mutations in this region can interfere with catalysis. Specifically, H324Y, E325A, H328Y, and E347A mutations inactivate the

aminopeptidase, whereas S327A decreases catalysis by about 15%. Y408F, N409S, and N409S/E410S mutations are not located in the active site but interfere with catalysis without completely inactivating the enzyme. See e.g. Table 2 at page 499. The specification identifies three active site segments, KKK from positions 161-163, the $HEXXHX_{18}E$ motif from 325-348, and a KGFCFVSYL moiety from 418-425. The rationale for the assignment of the KKK and KGFCFVSYL sequences as active site regions is unclear as these are identified by the prosite analysis in Fig. 4 as an amidation site and a putative RNA binding region, respectively. The specification provides general guidance as to what amino acid substitutions are deemed conservative in Table 1 at page 13 of the specification. No specific guidance is provided with regard to what specific amino acid substitutions are allowed at which positions, and no working example of any substitution mutation is provided. So, the prior art identifies as many as 20 single positions that can be mutated without eliminating catalysis, and one mutation in which 2 positions can be changed simultaneously, providing support for the position that at least 0.3% (2/650) of the amino acid positions in the protein can be simultaneously altered without eliminating aminopeptidase activity. In contrast, the instant claims would allow as much as 19% of amino acids to be altered simultaneously.

The prior art teaches that the effects of amino acid substitutions and deletions on protein function are highly unpredictable. Rudinger (In Peptide Hormones J.A. Parsons, Ed. University Park Press, Baltimore, 1976, page 6) teaches that "[t]he significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking

experimental study." Furthermore Ngo et al (In The Protein Folding Problem and Tertiary Structure Prediction, K. Merz Jr. and S. Legrand, Eds. Birkhauser, Boston, 1994, see page 492) teaches that "[i]t is not known if there exists an efficient algorithm for predicting the structure of a given protein from its amino acid sequence alone. Decades of research have failed to produce such an algorithm". One might argue that it would not be undue experimentation to express and assay polypeptides individually, and thereby empirically determine the function of each one. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and **their performance characteristics predicted by resort to known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added. Taken together, the teachings of the cited art indicate that the effects of mutations on protein structure are unpredictable and must be determined empirically. The prior art provides limited specific guidance as to which residues of an aminopeptidase B can be substituted and which cannot, but the few residues for which there are data fall far short of the extensive modifications that are embraced by the instant claims.

It interesting to note that Fukasawa (1999) recognized a high degree of homology between rat aminopeptidase B (ApB) and leukotriene A4 hydrolase (LTA4), an enzyme with both aminopeptidase and epoxide hydrolase activities. However, despite the fact that rat ApB was more closely related to LTA4 than to any other

aminopeptidase family member, Fukasawa showed that rat ApB had no epoxide hydrolase activity. Furthermore, when site directed mutations were made to the rat ApB to render it more similar to LTA4, these changes failed to produce epoxide hydrolase activity in the resulting enzymes. This provides further evidence of the unpredictability of protein structure/function relationships.

Finally, the claims broadly polypeptides with **any** aminopeptidase activity. As noted above under Written Description, the prior art teaches that aminopeptidase B enzymes catalyze the removal of N-terminal arginine and lysine residues, whereas there are many other aminopeptidases that have different specificities owing to different three-dimensional structures. However, the instant specification does not describe the structural characteristics that allow a particular aminopeptidase to catalyze a specific reaction. Further, the specification does not describe the structural characteristics of SEQ ID NO:1 that limit its activity to N-terminal arginines and lysines. As noted above the relationship between protein structure and function is complex and unpredictable. Absent guidance in the specification , one of skill in the art could not make fragments and variants of SEQ ID NO:1 that provide aminopeptidase activity other than that comprised by SEQ ID NO:1, without undue experimentation.

In view of the unpredictable nature of the protein structure/function relationships in general, the scarcity of data concerning aminopeptidase B structure and function, the lack of guidance or working examples in the specification regarding which amino acid residues can be substituted and which cannot while preserving aminopeptidase activity, and the lack of guidance concerning how to confer on SEQ ID NO:1 fragments and

variants aminopeptidase activity other than ApB activity, one of skill in the art could not make the invention as claimed without undue experimentation.

Response to Arguments

Applicant's arguments filed 1/12/06 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection of claims 12, 14, and 19 at pages 10-11 of the response.

Applicant's statement at page 11 of the response stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository, is sufficient to overcome the portion of the previous rejection directed to claims drawn to ATCC Accession No. PTA-2811.

Regarding the remaining enablement issues, Applicant argues that the rejection is overcome by limitation of the claims to polypeptides either at least 95% identical to SEQ ID NO:1 or encoded by nucleic acids at least 95% identical to SEQ ID NO:2. Applicant indicates that the specification teaches at page 13 how to provide functional variants of aminopeptidases by performing conservative substitutions. However, no specific guidance is provided with regard to what specific amino acid substitutions are allowed at which positions, and no working example of any substitution mutation is

provided. As stated in the rejection, the prior art identifies as many as 20 single positions that can be mutated without eliminating catalysis, and one mutation in which 2 positions can be changed simultaneously, providing support for the position that at least 0.3% (2/650) of the amino acid positions in the protein can be simultaneously altered without eliminating aminopeptidase activity. In contrast, the instant claims would allow as much as 19% of amino acids to be altered simultaneously. The Office has established the position that the art of protein structure function relationships is highly unpredictable, and Applicant has not shown otherwise. Applicant argues that the specification teaches assays for measuring aminopeptidase activity at page 24 and 25 of the specification. However, these assays are directed only to measuring lysine or arginine groups from N-termini. In contrast the claims are not limited to cleavage of any specific amino acid, and embrace any aminopeptidase activity. The specification has not taught how to make or assay aminopeptidases other than B-type aminopeptidases that cleave N-terminal K and/or R residues. Furthermore, the instant claims embrace a very large number of variants. Nineteen different substitutions can be made at each of as many as 123 different sites simultaneously. Even if one limited the mutable sites to 123 specific residues, then 19^{123} or 1.9×10^{157} variants are possible. There is no evidence of record that it is routine in the art to assay large numbers of aminopeptidases for activity, and there is insufficient guidance as to which mutations will preserve activity and which will not. In contrast, it is routine in the art to determine the minimal active fragment of a known sequence. As a result, Applicant's arguments are unpersuasive.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 12, 14 and 19 stand rejected under 35 U.S.C. 102(b) as being anticipated by Belhacene et al (Eur. J. Immunol. 23 (8), 1948-1955 (1993)) as evidenced by NCBI output retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=Protein&list_uids=40316915&dopt=GenPept on 8/25/05.

Belhacene taught a purified human aminopeptidase B. See abstract. Absent evidence to the contrary, the polypeptide of Belhacene has the sequence attributed to it in the attached NCBI output (gi:40316915), which cites Belhacene. The polypeptide in the NCBI output is 99% identical to SEQ ID NO:1. See alignment below. The "heterologous amino acid sequences" of claim 19 are considered to be those sequences in gi:40316915 that include the amino acids that differ from SEQ ID NO:1, i.e. any sequences including position 60 or position 645.

Thus Belhacene anticipates the claims.

ALIGNMENT FOR INSTANT SEQ ID NO:1 AND gi:40316915

"query" = SEQ ID NO:1
"Sbjct" = gi:40316915

gi|40316915|ref|NP_064601.3| arginyl aminopeptidase (aminopeptidase B) [Homo sapiens] Length=650

Score = 2104 bits (4955), Expect = 0.0
Identities = 648/650 (99%), Positives = 649/650 (99%), Gaps = 0/650 (0%)

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Query  1    MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS  60
            MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS
Sbjct  1    MASGEHSPGSGAARRPLHSAQAVDVASASNFRAFELLHLHLDLRAEFGPPGPGAGSRGLS  60

Query  61   GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPAEPVSFYTQPFSHYGQ  120
            GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPAEPVSFYTQPFSHYGQ
Sbjct  61   GTAVLDLRCLEPEGAAELRLDSHPCLEVTAAALRRERPGSEEPPAEPVSFYTQPFSHYGQ  120

Query  121  ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGQAVLNRAFFP  180
            ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGQAVLNRAFFP
Sbjct  121  ALCVSFPQPCRAAERLQVLLTYRVGEGPGVCWLAPEQTAGKKKPFVYTQGQAVLNRAFFP  180

Query  181  CFDTPAVKYKYSALIEVPDGFTAVMSASTWEKRGPNKFFFQMCQPIPSYLIALAIGDLVS  240
            CFDTPAVKYKYSALIEVPDGFTAVMSASTWEKRGPNKFFFQMCQPIPSYLIALAIGDLVS
Sbjct  181  CFDTPAVKYKYSALIEVPDGFTAVMSASTWEKRGPNKFFFQMCQPIPSYLIALAIGDLVS  240

Query  241  AEVGPRSRVWAEPCLIDAANEEYNGVIEEFLATGEKLFGPYVWGRYDLLFMPPSFPFGGM  300
            AEVGPRSRVWAEPCLIDAA EEYNGVIEEFLATGEKLFGPYVWGRYDLLFMPPSFPFGGM
Sbjct  241  AEVGPRSRVWAEPCLIDAAKEEYNGVIEEFLATGEKLFGPYVWGRYDLLFMPPSFPFGGM  300

Query  301  ENPCLTFVTPCLLAGDRSLADVIIHEISHSWFGNLVTNANWGEFWLNEGFTMYAQRRIST  360
            ENPCLTFVTPCLLAGDRSLADVIIHEISHSWFGNLVTNANWGEFWLNEGFTMYAQRRIST
Sbjct  301  ENPCLTFVTPCLLAGDRSLADVIIHEISHSWFGNLVTNANWGEFWLNEGFTMYAQRRIST  360

Query  361  ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKLRVKIEPGVDPDDTYNETPYEKGFCF  420
            ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKLRVKIEPGVDPDDTYNETPYEKGFCF
Sbjct  361  ILFGAAYTCLEAATGRALLRQHMDITGEENPLNKLRVKIEPGVDPDDTYNETPYEKGFCF  420

Query  421  VSYLAHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDIIPGFEFD  480
            VSYLAHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDIIPGFEFD
Sbjct  421  VSYLAHLVGDQDQFDSFLKAYVHEFKFRSILADDFLDFYLEYFPELKKKRVDIIPGFEFD  480

Query  481  RWLNTPGWPPYLPDLSPGDSLMKPAEELAQLWAAEELDMKAIEAVAISPWKTYQLVYFLD  540
            RWLNTPGWPPYLPDLSPGDSLMKPAEELAQLWAAEELDMKAIEAVAISPWKTYQLVYFLD
Sbjct  481  RWLNTPGWPPYLPDLSPGDSLMKPAEELAQLWAAEELDMKAIEAVAISPWKTYQLVYFLD  540

Query  541  KILQKSPLPPGNVKKLGDTYPSISNARNAELRLRWGQIVLKNDHQEDFWKVKEFLHNQGK  600
            KILQKSPLPPGNVKKLGDTYPSISNARNAELRLRWGQIVLKNDHQEDFWKVKEFLHNQGK
Sbjct  541  KILQKSPLPPGNVKKLGDTYPSISNARNAELRLRWGQIVLKNDHQEDFWKVKEFLHNQGK  600

Query  601  QKYTLPLYHAMMGGSEVAQTLAKETFASTASQLHSNVVNYVQQIIAPKGS  650
            QKYTLPLYHAMMGGSEVAQTLAKETFASTASQLHSNVVNYVQQI+APKGS
Sbjct  601  QKYTLPLYHAMMGGSEVAQTLAKETFASTASQLHSNVVNYVQQIVAPKGS  650
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Response to Arguments

Applicant's arguments filed 1/12/06 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection of claims 12, 14, and 19 at pages 12 and 13 of the response. Essentially, Applicant argues that the Belhacene does not anticipate the claims because Belhacene does not disclose any sequence, and the NCBI record referencing Belhacene (gi:40316915) was not known in the art at the time of filing. This is unpersuasive. Belhacene purified a human amino peptidase B. The sequence of that protein is inherent. Applicant has presented no evidence that the protein purified by Belhacene is not the protein set forth in gi:40316915. Note that the NCBI records referred to by Applicant as gi:13443031 and gi:9910198 do not cite the Belhacene paper, whereas the gi: 40316915 record does. Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an Applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, 441 F.2d 660, 169 USPQ 563 (CCPA 1971). Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430,

433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). The rejection is maintained.

Conclusion

No claim is allowed.

Claims 15-18 and 20 are objected to because they depend form a rejected claim but would be allowable if rewritten as independent claims including all of the limitations of the claims from which they depend. Claims 21 and 22 are objected to because they depend form a rejected claim but would be allowable if amended to overcome the objections set forth above on page 3, and if rewritten as independent claims including all of the limitations of the claims from which they depend. for the same reasons as well as those set forth above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang, can be reached at (571) 272-0811. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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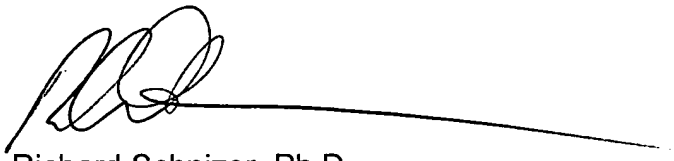

Richard Schnizer, Ph.D.
Primary Examiner
Art Unit 1635